American Cancer Society Second National Conference on Cancer Genetics

Supplement to ***Cancer***

The Genetics of Hereditary Melanoma and Nevi

1998 Update

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Presented at the American Cancer Society Second National Conference on Cancer Genetics, San Francisco, CA, June 26–28, 1998.

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Received May 25, 1999;accepted June 3, 1999.

Although the first English-language report of melanoma in 1820 contained a description of a melanoma-prone family, it was 1983 before formal genetic analysis suggested an autosomal dominant mode of inheritance for both melanoma and the then newly described melanoma precursor, dysplastic nevi (DN). Subsequent genetic studies have assumed this model to be correct, although when viewed in aggregate, the data are inconsistent.

The first proposed melanoma gene (*CMM1*) was mapped to chromosome 1p36. This gene assignment has *not* been confirmed. A second melanoma gene, designated *CMM2*, has been mapped to chromosome 9p21. This gene assignment *has* been confirmed, and the cell cycle regulator *CDKN2A* has been proposed as the candidate gene. Germline mutations in this gene have been identified in about 20% of melanoma-prone families that have been studied to date. Pancreatic cancer occurs excessively in melanoma families with germline mutations in *CDKN2A*.

Germline mutations in the cyclin-dependent kinase gene *CDK4* (chromosome 12q14) have been described in three melanoma families. This finding represents a third melanoma gene but one that accounts for only a tiny fraction of all hereditary melanoma. Recently, a familial melanoma-astrocytoma syndrome has been reported. Large germline deletions of 9p21 occur in these families, with the p19 gene implicated in its pathogenesis. At present, clinical predictive genetic testing for mutations in the *CDKN2A* gene is available commercially, but its use has been limited by uncertainty as to how test results would affect the management of melanoma-prone family members. Currently, management recommendations include monthly skin self-examination, clinical skin examination once or twice yearly, a low threshold for simple excision of changing pigmented lesions, moderation of sun exposure, and appropriate use of sunscreens.

A heritable determinant for total nevus number has been suggested by twin studies. Other data suggest the presence of a major gene responsible for "total nevus density" in melanoma-prone families. Approximately 55% of the mole phenotype in multiplex melanoma families was explained by this proposed gene. An autosomal dominant mode of inheritance has been proposed for DN, and data exist to suggest that DN may be a pleiotropic manifestation of the 1p36 familial melanoma gene. However, there clearly are melanoma-prone families that do not express the dysplastic nevus trait, and some of the families linked to *CDKN2A* also present with dysplastic nevi. Several studies have shown a surprisingly high prevalence of DN on the skin of family members of probands with DN. In light of the extensive evidence documenting that persons with DN (both sporadic and familial) have an increased *prospective* risk of melanoma, these family studies suggest that relatives of persons with DN should be examined for both DN and melanoma.

Genetic determinants play a major role in the pathogenesis of normal nevi, DN, and melanoma. Identifying the molecular basis of these genetic events promises to enhance melanoma risk-reduction strategies and, ultimately, reduce melanoma-associated mortality. ***Cancer*** **1999;86:2464–77.** *© 1999 American Cancer Society.*

KEYWORDS: hereditary melanoma, dysplastic nevi, *CDKN2A*, *CDK4*, melanoma/astrocytoma syndrome.

The first English-language report that described the entity we now know as cutaneous malignant melanoma was, in fact, a familial occurrence of the disease.[1] These observations went unnoticed for 132 years, until Cawley[2] made a similar observation in 1952. Both Norris and Cawley commented that their families displayed numerous nevi. Over the next 25 years, a series of anecdotal case reports appeared (reviewed in Greene and Fraumeni[3]) in which multiple-case melanoma families were reported as interesting curiosities. A positive family history of melanoma has been reported in 8 to 14% of melanoma patients; familial cases tended to be younger, to have higher numbers of moles, and to develop multiple primary melanomas.[4,5] An overview analysis of eight melanoma case–control studies reported a melanoma relative risk of 2.2 in persons who reported at least one affected first-degree relative, an effect that was independent of age, nevus count, hair and eye color, and freckling.[6] However, formal genetic analysis is required to prove the existence of a mendelian basis for a particular disease. For melanoma, this work began in the late 1970s.

GENETICS OF MELANOMA

CMM1

Fourteen melanoma-prone kindreds were studied by investigators at the National Cancer Institute (NCI) and the University of Pennsylvania (NCI/Penn). Distinguishing features of the hereditary melanoma syndrome in the NCI/Penn series included a younger than average age at melanoma diagnosis, a striking predisposition toward multiple primary melanomas, and the presence of multiple, clinically atypical moles that were designated "dysplastic nevi"[7–10] (Table 1). In this cohort, nearly all family members with cutaneous malignant melanoma (CMM) also had dysplastic nevi (DN) on their skin, and during prospective follow-up, new melanomas were diagnosed *only* in family members with DN. These investigators proposed that DN were both markers that identified those family members who were at increased risk of CMM and precursor lesions from which the majority of newly diagnosed melanomas evolved. These findings were thought to be analogous to those previously made in families with colonic polyposis and colorectal cancer.

Segregation analysis suggested that when the disease trait was defined as either CMM or DN, an autosomal dominant model best fit the pattern in these families,[11] a finding that has been confirmed.[12] The NCI/Penn group found that the distribution of the CMM and DN was so tightly linked that they appeared to represent pleiotropic manifestations of the same gene.[13] However, the Seventh Genetic Analysis Workshop reviewed primary data from all previously-reported melanoma-prone families and concluded that "dominant inheritance was strongly rejected."[14] Nonetheless, familial melanoma investigators have continued to base their analyses on the presumption that this trait is inherited in an autosomal-dominant fashion.

TABLE 1
Clinical Features of Hereditary and Sporadic Melanoma

Characteristic	Hereditary Melanoma	Sporadic Melanoma
Median Age (yrs)		
Male	36	57
Female	29	50
Diagnosis before age 20	10%	2%
Male/female ratio	1.4	1.2
Multiple primary melanomas	30%	4%
Melanoma subtype (predominant)	SSM	SSM
Presence of dysplastic nevi	Majority	~30%
Positive family history of melanoma	100%	~10%
Nevus at edge of melanoma (histologic)	85%	50%

SSM: superficial spreading melanoma.

The first linkage analysis was performed by the NCI/Penn group without an a priori hypothesis as to where the melanoma gene might be. This genomic search identified moderately strong evidence of linkage between CMM/DN and the Rh blood group locus, known to be on the short arm of chromosome 1.[11] Additional analysis led to the conclusion that a CMM/DN gene was located on chromosome 1p36.[15,16] The estimated penetrance of this gene, designated *CMM1,* was 82% by age 72.[17] As yet, no candidate gene from this chromosomal region has been identified. In fact, numerous attempts by other investigators of familial melanoma have failed to corroborate the gene assignment proposed by the NCI/Penn team.[18–21]

Both etiologic and diagnostic heterogeneity have been suggested as explanations for this discrepancy. In the nonconfirming series, some families were multiplex for melanoma only (no DN were present), whereas others were multiplex for DN only (no CMM were present). Clearly, there are CMM-prone families in which DN do not occur, and a different genetic locus may be operative in those kindred. Furthermore, a founder effect was observed in some of the Dutch families, suggesting that they might represent a genetic isolate.[22] Diagnostic inconsistencies in the definition of DN may have contributed to the failure of other investigators to confirm the 1p36 gene assignment. For example, the Utah investigators did not require cytologic atypia of melanocytes to make a histologic diagnosis of DN.[19] As a result, the preva-

lence of so-called DN became so high that the genetic model did not fit. Further difficulties with the 1p36 gene assignment were encountered when some of the families linked to this locus were found to have mutations in the *CDK4* gene (see below). Finally, despite intensive effort, no candidate gene has been identified on 1p36. Thus, at present, the validity of this gene assignment is in serious doubt and may prove to be erroneous.

CMM2

Recent observations have shifted the focus of familial melanoma research to a second gene site, located on chromosome 9p. On the basis of cytogenetic studies performed on melanoma cell lines, which pointed to chromosome 9p as an area of frequent cytogenetic abnormality,[23–25] the Utah group performed a linkage analysis in 11 CMM pedigrees. DN were not included in their analysis. Multipoint linkage analysis provided strong evidence for a partially penetrant, dominant melanoma susceptibility locus (designated *CMM2*) on 9p21.[26,27] The penetrance for this gene was estimated to be 53% by age 80, and gene carriers were found to have higher nevus counts and nevus densities than nongene carriers.[28] Among gene carriers, persons with melanoma had more sun exposure than those without melanoma, suggesting a genetic-environmental interaction in melanoma susceptibility within these families.[28] Other data suggest an interaction between sunlight exposure and 9p21 mutation status in the development of hereditary melanoma. In families linked to 9p21, the cumulative melanoma incidence was 21 times higher among subjects born after 1959 compared with those born before 1900.[29] This increasing penetrance of the *CMM2* gene was attributed to an interaction between sunlight exposure and mutations at this locus. In a separate study of 13 families with *CDKN2A* (see below) mutations, the risk of melanoma was increased by pale complexion and measures of solar injury to the skin, even after controlling for mutation status.[30] Sun-related exposures seemed to increase the risk of melanoma beyond that accounted for germline mutations alone. This suggests that members of such families may be able to reduce their melanoma risk by limiting exposure to the sun.

The 9p21 gene assignment for the CMM2 locus has been confirmed.[16,22,31–33] The NCI group found that some of their families were linked to 9p, whereas others remained linked to 1p.[16] They found statistically significant genetic heterogeneity in their cohort of families, supporting the existence of at least *two* melanoma-susceptibility genes, and significant linkage to the 9p21 locus when DN were included in the analysis. Dutch investigators suggested that evidence of linkage between *CMM2* and 9p21 became stronger when DN were included in the model.[22,32] British investigators evaluated six multiple-case melanoma families and found evidence supporting linkage to 9p21 in three.[33] One family clearly was not linked to 9p21 (1p36 was not evaluated in this study), providing further support for the existence of more than one familial melanoma gene.

The *CMM2* gene has been identified as *CDKN2A*, also known as *MTS1*; it encodes a protein designated "$p16^{INK4a}$."[34] This protein binds and inhibits the cyclin-dependent kinases CDK4 and CDK6. When active, these kinases phosphorylate the retinoblastoma protein, permitting resting cells to proliferate and divide. Thus, mutations in p16 could facilitate aberrant or unchecked cellular proliferation. The NCI group described germline p16 mutations in 33 of 36 melanoma patients from nine different families.[35] In addition, these mutations were not observed in melanoma patients from families linked to the 1p36 melanoma locus, again supporting the hypothesis that there are at least two melanoma susceptibility genes. The mutant p16 proteins they identified were functionally impaired in their ability to inhibit the growth-promoting activity of cyclin/cyclin-dependent kinase complexes in vitro.[36] Studies of hereditary melanoma cell lines from the same families revealed loss of the wild-type *CKDN2A* allele, thereby fulfilling criteria required to classify this gene as a tumor suppressor gene. Thus, some hereditary melanomas develop when cells inherit a mutant *CDKN2A* allele and then lose the wild-type allele in a secondary, somatic event.

Utah investigators analyzed *CDKN2A* coding sequences in 13 families linked to 9p and in 38 additional melanoma-prone families.[37] In only two families were potential predisposing mutations found. The authors concluded that "either the majority of mutations fall outside the CDKN2A coding sequence or that CDKN2A is not MLM."[37] However, nearly 400 CMM families have now been evaluated with regard to their *CDKN2A* status (reviewed by Haluska and Hodi[38]). Overall, 18% of families tested have been found to carry germline mutations in this gene. If one looks at the subset of tested families in which there was a significant prior probability of finding a mutation, the proportion in which germline alterations were found rose to 37%. Both the Utah and NCI data sets contain families that are strongly linked to 9p21 but that have (as yet) *no* detectable *CDKN2A* mutations. Of interest in this regard is the recognition that *CDKN2A* can encode two distinct proteins depending on which of two alternative first exons (E1α or E1β) is transcribed. When E1α is transcribed, the resulting protein is $p16^{INK4a}$. When E1β is transcribed, exons 2 and 3 are

translated in an alternate reading frame and the protein p19 ^{ARF} is encoded.[39] The latter protein has no amino acid homology with p16^{INK4a}. It does induce cell cycle arrest through a CDK-independent mechanism by interacting with p53. Its role in hereditary melanoma is uncertain at present. Three analyses, including a total of 176 melanoma families, have specifically looked for mutations in p19^{ARF}, and none was found.[40–42]

Additional support for the candidacy of *CDKN2A* derives from studies assessing the risk of cancers other than melanoma in melanoma-prone families. Some investigators have reported no increase in the risk of nonmelanoma cancers,[17,43] whereas others have suggested that such excesses do occur, with pancreatic cancer being a site of particular interest.[44,45] A population-based survey of second malignancies in patients diagnosed first with malignant melanoma revealed a nearly twofold excess in the risk of subsequent pancreatic cancer, particularly in patients diagnosed with melanoma when younger than age 50.[46] Goldstein et al.[47] compared the incidence of pancreatic cancer in 10 families with p16^{INK4} mutations with that of 9 families with normal p16^{INK4} function. The relative risk of pancreatic cancer was 22 in the former (7 observed versus 0.32 expected), whereas *no* pancreatic cancer was observed in the latter families.[47] A second report of a single family with both melanoma and pancreatic cancer and a germline *CDKN2A* mutation supports this observation.[48] These data suggest that the development of pancreatic cancer in melanoma-prone families may require a mutation in the *CDKN2A* gene.

Finally, knowing that patients with hereditary melanomas are prone to developing multiple primary melanomas led Monzon et al.[49]to test a series of 33 patients with more than one melanoma (and *no* family history of melanoma) for *CDKN2A* mutations. Five (15%) patients had germline mutations;in three families the same mutation was found in other family members, and in two, previously unknown family histories of melanoma were discovered. Patients with multiple primary melanomas may warrant investigation in search of a genetic predisposition to their cancers.

CMM3

A third melanoma gene candidate has emerged from studies of a melanoma tumor cell line in which a mutation in the cyclin-dependent kinase 4 (*CDK4*) gene was found.[50] As noted above, this protein (mapped to chromosome 12q14) is one step downstream from *CDKN2A* in its cell-cycle pathway. Studies of families with normal p16 function led to the discovery of two kindred with an identical *CDK4* mutation.[51] A third *CDK4* mutation was found in a separate study.[52] Several hundred additional families have been screened and found not to carry *CDK4* mutations. Thus, this melanoma susceptibility gene (*CMM3*) accounts for only a tiny fraction of all hereditary melanomas. The *CDK4* mutations described in these families result in activation of this protein by interfering with its binding to, and thus inhibition by, p16. Therefore, like *RET* (MEN2A 2B and medullary carcinoma of the thyroid) and *MET* (papillary renal cell carcinoma), *CDK4* functions as a dominant oncogene, *not* a tumor suppressor gene. As mentioned earlier, the discovery of this genetic abnormality has contributed to the uncertainty over the 1p36 melanoma gene assignment, because the two families in which Zuo et al.[51] found this mutation were among those previously reported to be linked to 1p36.

Other Melanoma Genes

Recently, two striking families have been reported in which both cutaneous melanoma and primary glial tumors (astrocytoma) have occurred excessively.[53,54] Support for the existence of such an entity was provided by a study in which the prevalence of nervous system cancers as second cancers was analyzed in a serious of more than 900 melanoma patients and their relatives.[55] A surprising number of neural tumors (diverse histologies) was observed. In contrast, *no* brain tumors were observed in the two studies that quantitatively assessed the risk of cancers other than melanoma in hereditary CMM families.[17,45] The two multiplex families have now been subjected to detailed molecular genetic analysis.[56] Both families have had neurofibromatosis excluded by sequencing of the *NF1* gene. Both families were linked to 9p21 in linkage analysis, but in neither could germline mutations in either p15 or p16 be identified by direct sequencing. Both families have been found to have large genomic deletions of 9p21. In one, the deletion encompasses p15, p16, and p19; in the second, p15 is spared.[56] The results are interpreted as suggesting a role for p19 as a bonafide tumor suppressor and that inactivation of the contiguous p16 and p19 genes may account for the specific tumor spectrum observed in these families.

Could there be still more melanoma-susceptibility genes? The rapidly unfolding stories of familial breast cancer and hereditary nonpolyposis colon cancer provide ample precedent for such a possibility. It often has been speculated that a melanoma-susceptibility gene might be linked to the HLA complex on chromosome 6p, although the largest reported series of families in which linkage between HLA and either melanoma or melanoma plus DN was studied yielded

TABLE 2
Current Melanoma Susceptibility Loci

Designation	OMIM number	Chromosome	Gene	Mechanism	Clinical features
CMM1	155600	1p36	?	?	Strong association with dysplastic nevi
CMM2	600160	9p21	*CDKN2A*	Tumor suppressor gene	Excess risk of pancreatic cancer
CMM3	123829	12q14	*CDK4*	Dominant oncogene	Very rare
CMM4 (?)	155755	9p21	?$p19^{ARF}$	? Contiguous tumor suppressor disorder	Families prone to both CMM and primary glial tumors

CMM: cutaneous malignant melanoma; OMIM: Online mendelian inheritance in man (www3.ncbi.nlm.gov/OMIM/searchomim.html).

strong evidence *against* linkage.[57] Recently, the Queensland group has reopened this question with a linkage analysis of 16 Australian melanoma-prone families that yielded moderate evidence in favor of linkage (multipoint lod score = 1.64).[58] Whether a melanoma gene lies within or near the HLA gene complex remains to be determined. Cytogenetic studies have suggested that one or more genes on chromosomes 2, 3, 10, and 11 also may have a role in melanoma development,[59] but no definitive evidence has emerged. It seems probable that additional melanoma-susceptibility genes will be found as the molecular genetic tools required for such studies become increasingly sophisticated and powerful. The four loci of greatest current interest are summarized in Table 2.

GENETICS OF NEVI

The genetic basis of nevi is less well understood. With regard to nevi in general, a study of counted nevi among 23 monozygotic and 22 dizygotic twin pairs revealed a strong correlation in the total number of nevi observed in the monozygotic twins ($r = 0.83$) but not among dizygotic twins ($r = -0.24$).[60] A precise genetic model could not be specified because of the study design, but the data suggested a strong inherited basis for total nevus count.

The Utah group provided additional data on the inheritance of nevi by analyzing their families for total nevus number and total nevus density. The latter is a derived variable computed from mole size and number. This analysis suggested the presence of a major gene that accounted for about 55% of the mole phenotype in the multiple-case families but no evidence of a major "mole gene" in the single-case families.[61] Total nevus density fit a mendelian pattern better than does total nevus number. Because dysplastic nevi are, by definition, larger and more numerous than normal nevi, "total nevus density" may be a surrogate indicator for the DN phenotype.

With reference to DN, the original analyses by the NCI/Penn team suggested an autosomal dominant mode of inheritance[11,15,16] and further indicated that CMM and DN might be pleiotropic manifestations of the same gene, *CMM1*.[13] As noted above, some investigators have been unable to corroborate the importance of DN in their melanoma families,[19–21] whereas others have confirmed the etiologic importance of DN in their kindreds.[22,62] Systematic evaluation of the reproducibility and accuracy of the histopathologic diagnosis of DN has largely supported the ability to apply established criteria successfully,[63–67] although occasional exceptions are apparent.[68,69] In the most rigorous of these studies, using the presence of preselected criteria as a condition for the diagnosis of DN, values for sensitivity, specificity, and positive and negative predictive values were 0.86, 0.91, 0.96, and 0.73, respectively.[66] The current working definition of DN requires both a size of 5 mm or more and the presence of a macular component in the lesion (the "obligatory criteria") plus at least two of the following features: (1) variable pigmentation; (2) irregular, asymmetric outline; or (3) indistinct borders[70] (Fig. 1). In my opinion, failure to apply rigorously the well described histologic criteria for DN, especially the requirement for readily recognizable melanocytic atypia, accounts for much of the controversy regarding the putative difficulties in rendering the pathologic diagnosis of DN.

Additional genetic and epidemiologic studies have used DN rather than melanoma as the starting point. A careful study of melanocytic nevi in a consecutive series of patients seen in a large, private dermatology practice[71] provided a cohort of patients unselected for family history of melanoma within which a nested case–control study was performed. Twenty-five patients with DN were matched to 28 controls who lacked DN, and all willing first-degree relatives of both cases and controls were examined for DN.[72] DN were found among the relatives of 80% of cases and in 4% of controls. The relative risk of having DN was 7.2 if one or more relatives had DN. Three of the cases in the

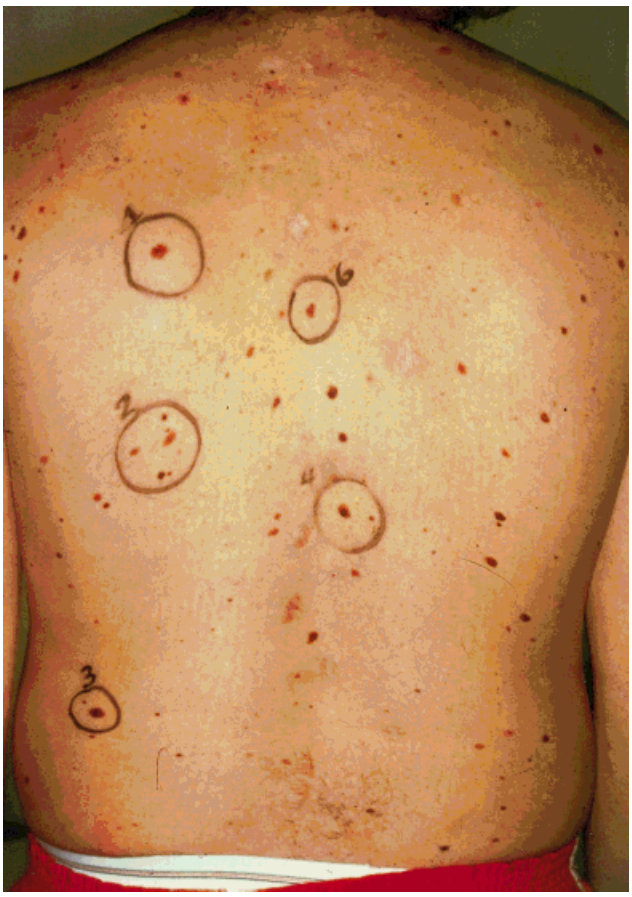

FIGURE 1. Hereditary dysplastic nevi. This 26-year-old man is the proband of a family with numerous cases of early-onset cutaneous melanoma. The patient has had multiple primary melanomas and displays the characteristic phenotype of an individual with florid dysplastic nevi. He had a profusion of large, irregularly shaped, variably pigmented nevi, many of which have a macular component.

families multiplex for DN were found to have a first-degree relative with melanoma. This report suggested that relatives of unselected persons with DN are themselves likely to have DN and may also be at increased risk of melanoma. This same cohort was also subjected to a formal genetic analysis.[73] The estimated segregation ratio for a hypothetical DN gene was 0.52, consistent with an autosomal dominant mode of inheritance.

A skin examination was performed on 156 living family members of 31 probands initially classified as having sporadic, histologically verified DN.[74] These persons were classified as "sporadic DN" because they *reported* no cases of either CMM or DN among their relatives. After the relatives were actually examined, 60% of the probands were found to have one or more relatives with DN! One relative was diagnosed as having malignant melanoma in situ at the time of the examination. Using data from a concurrent survey of 400 general population controls, Crijns et al.[74] estimated that relatives of DN probands were four times more likely than unselected patients to have DN. They concluded that "screening of family members of patients with DNS without familial melanoma would appear to be useful . . . ." One source of difficulty in evaluating the familial aggregation of DN is evidence suggesting that sunlight may play a role in their induction.[75] It is likely that there will be at least some environmentally induced DN phenocopies among cases of DN that cluster in families.

British investigators examined a series of 266 melanoma patients and 305 controls for the presence of what they designated the "atypical mole syndrome" (AMS). A formal scoring system was used to define AMS,[76] which is an alternative term for DN syndrome. They offered skin screening to the relatives of study subjects found to have AMS. In this study, 39% of the 91 relatives examined had AMS, compared with 15% of melanoma patients and 2% of the normal population.[62] Although a formal genetic analysis of nevus distribution in this cohort has not been reported, the authors believed that the "mode of inheritance was consistent with a single autosomal dominant gene, with the AMS phenotype and melanoma as two possible expressions of the same gene," echoing the observations reported by Bale et al.[13]

The role of the various melanoma susceptibility genes described above in the development of dysplastic nevi is uncertain. The original work by the NCI group had suggested that the melanoma and DN phenotypes might be pleiotropic manifestations of the 1p36 melanoma gene.[13] This has been called into question by the discovery of germline mutations in *CDK4* in two of the NCI families that had been linked to the 1p36 locus.[51] With regard to the CDKN2A locus, the data are again mixed. In the Dutch series of melanoma families, lod scores for linkage to 9p *increased* when DN were included in the model.[22] In the NCI series, evidence for 9p linkage was *weakened* by including DN in the analytic model.[35] In that series, only 30% of DN patients were found to have *CDKN2A* mutations. A family reported from Spain showed a similar pattern of inconsistent mutations in DN patients.[77] On the other hand, *CDKN2A* mutations have been suggested to be an important early genetic event in the evolution of sporadic DN.[78] Some of the inconsistency may be the result of DN phenocopies within the melanoma families because the prevalence of DN in the general population averages approximately 11% (Table 3). This aspect of the hereditary melanoma story remains confused; more work is required to clarify the

TABLE 3
Prevalence of Dysplastic Nevi in Melanoma Case–Control Studies

Author	No. of cases	No. of controls	Variable	Dysplastic nevi (%)		No. of dysplastic nevi	Relative risk
				Cases	Controls		
Nordlund et al.[79]	296	145	Atypical nevi	34	7	—	7.4
Cristofolini et al.[80]	103	205	Dysplastic nevi	6	4	—	1.4
Swerdlow et al.[81]	180	197	Large nevi	31	11	—	3.9
						0	1.0
						1–4	5.2
						5+	5.7
Roush et al.[82]	246	134	Dysplastic nevi	34	7	—	7.6
Kelly et al.[83]	121	139	Dysplastic nevi	55	17	—	6.0
						0	1.0
						1–5	3.8
						6+	6.3
Grob et al.[84]	207	295	Clinically atypical nevi	34	21	—	1.9
Halpern et al.[85]	105	181	Dysplastic nevi	39	7	—	6.8
Stierner et al.[86]	121	310	Dysplastic nevi	56	19	—	5.4
Newton et al.[76]	266	305	Atypical mole syndrome	15	2	—	7.5
Garbe et al.[87]	496	476	Clinically atypical nevi	37	17	—	2.8
						0	1.0
						1–4	1.6
						5+	6.1
Holly et al.[88]	452	930	Large nevi	NA	NA	0	1.0
						1–3	4.5
						4–7	6.1
						8+	16.7
Bataille et al.[89]	426	416	Atypical mole syndrome	16	2	—	10.4
						0	1.0
						1	3.5
						2–3	5.4
						≥4	23.7
Grulich et al.[90]	259	281	Atypical nevi	36	21	0	1.0
						1–2	1.6
						3–4	3.7
						5+	9.0
Tucker et al.[70]	716	1014	Dysplastic nevi	40	10	0	1.0
						1	2.3
						2–4	7.3
						5–9	4.9
						≥10	12

NA: not available.

relationship of DN to the melanoma susceptibility genes.

In summary, formal genetic analysis provides significant support for the hypothesis that both the phenotype of common acquired nevi and the phenotype of DN are under genetic control. The mode of inheritance is not well understood for ordinary nevi, although an autosomal-dominant model seems most plausible for DN. Clearly, much work remains to be done for both nevus phenotypes. Meanwhile, it seems evident that relatives of patients with DN are at increased risk for DN (and probably melanoma) themselves. Therefore, they constitute a subset of the general population on whom melanoma risk-reduction and screening activities can be focused.

EVIDENCE LINKING DYSPLASTIC NEVI TO MELANOMA RISK

A review article has summarized a broad range of clinical and biologic data that supported the validity of the DN concept.[91] Currently, two sets of data are most compelling in this regard: (1) DN prevalence surveys performed in melanoma case–control studies, and (2) *prospective* surveillance of various cohorts of patients with DN for the development of melanoma.

With reference to the former, at least 14 case–

TABLE 4
Prospective Melanoma Diagnosis in Familial Dysplastic Nevi

Author	No. of families	No. of patients	Prospective CMM (No.)	Mean thickness (mm)	Clark level I	Clark level II	DNS (%)	CMM relative risk[a]
Greene et al.[9]	14	(series updated by Tucker et al.,[17] see below)						
Vasen et al.[94]	9	NA	20	0.54	7	8	NA	NA
Rigel et al.[95]	NA	105	11	0.43	7	4	100	167
Masri et al.[96]	264	555	28	0.52	5	12	NA	NA
MacKie et al.[97]	6	7	8	0.69	2	6	100	444
Tucker et al.[17]	23	470	77	NA	30		100	DN, 85 DN/CMM 229
Carey et al.[98]	311	710	40	0.56	77% (level I and II)		100	DN, 116 DN/CMM 964
Tiersten et al.[99]	NA	105	3	NA	NA	NA	100	53

CMM: cutaneous malignant melanoma; DN/CMM: dysplastic nevus patients with melanoma diagnosed before entry into study; DNS: dysplastic nevus syndrome; NA: not available.
[a] Computed using only invasive melanomas.

control studies have been published in which both cases and controls were examined for the presence of DN or clinically atypical nevi.[70,76,79,80–88,92,93] In these studies, DN were defined and counted in different ways, but in all cases, the diagnoses were established *clinically*. Thus, the debate over histologic criteria for DN diagnosis becomes irrelevant to these results. With one exception,[80] DN have emerged from these analyses as one of the most important melanoma risk factors yet identified. In these studies, DN act independently of other identifiable melanoma risk factors, such as hair and eye color, complexion type, tendency to freckle, history of sunlight exposure, family history, and so forth. On average, 33% of patients with melanoma had DN, compared with 11% of controls (Table 3). The summary relative risks for melanoma conferred by the presence of DN ranged from 1.0 to 10.4 (median, 5.4), and several studies documented increasing risk of melanoma as the number of DN or atypical nevi increased (Table 3). The most definitive of these studies is that recently published by Tucker et al.,[70] which demonstrated the relationship between dysplastic nevi and melanoma risk quite convincingly and rigorously. In the aggregate, these studies provide strong evidence that DN, variably but *clinically* defined, are a potent melanoma risk factor.

The best evidence regarding the validity of the DN concept derives from observations that document the excess risk of melanoma in various cohorts of patients with DN who have been monitored *prospectively* for new melanomas. Seven prospective cohorts of patients with *familial DN* have been reported (Table 4).[9,17,94–99] Noteworthy observations in these studies include the nearly exclusive occurrence of new melanomas in family members with DN, the remarkably increased relative risks for melanoma (particularly in DN patients who had a melanoma diagnosed before the prospective phase of study), the striking number of melanomas diagnosed at an in situ stage (35% of all prospectively diagnosed melanomas), and the relatively thin (i.e., biologically "early") average melanoma depth at diagnosis. These findings demonstrate clearly that the presence of DN identifies specific family members who are at increased risk of melanoma and imply that the prognosis for those family members whose melanomas are diagnosed as a consequence of active surveillance should be excellent.

Finally, just as it has become apparent that the occurrence of DN is not confined to melanoma-prone families (Table 3), so too has it now been *prospectively* demonstrated in at least eight studies that DN patients without an obvious family history of melanoma and DN patients selected without regard to their family history are at increased risk of melanoma (Table 5). The findings parallel those seen in patients with familial DN, except that the relative risks for melanoma are lower. The study of Kelly et al.[104] is particularly interesting in that it showed clearly the value of clinical photography in the follow-up of DN patients: 11 of 20 prospectively diagnosed melanomas were identified because of changes evident when compared with baseline photographs. In addition, 13 of the 20 new melanomas arose as *new* lesions rather than from preexisting DN. Thus, contrary to the views of some,[68,69,105] DN *do* provide a means of identifying persons at increased risk for melanoma, even outside the context of melanoma-prone families.[106] Furthermore, the recognition of this class of atypical melanocytic lesions has permitted the formulation of a rational, biologically plausible model of the progression of melanocytic tumors.[107]

TABLE 5
Prospective Melanoma Diagnosis in Unselected Patients with Dysplastic Nevus

Author	Prior CMM	No. of subjects	Prospective CMM (No.)	Mean thickness (mm)	Clark level		CMM relative risk[a]
					I	II	
Rigel et al.[95]	No	281	4	0.88	3	1	16
	Yes	66	3	0.26	2	1	36
Tiersten et al.[99]	No	157	4	NA	NA	NA	53
	Yes	95	4	NA	NA	NA	74
Halpern et al.[100]	No	89	2	0.52	0	2	154 per 100,000 per year
MacKie et al.[97]	No	85	9	0.96	4	5	93
	Yes	24	3	0.78	1	4[b]	91
Kang et al.[101]	No	84	2	0.75	NA[c]	2	NA
Marghoob et al.[102]	No	124	10	NA	NA	NA	63
	Yes	163		NA	NA	NA	90
Schneider et al.[103]	No	267	5	NA	NA	NA	47
Kelly et al.[104]	No	215	9[d]	<0.60	8	12	46
	Yes	63	7	<0.60			

CMM: cutaneous malignant melanoma; NA: not available.

[a] Computed using only invasive melanomas.

[b] Two patients each developed two primary melanomas.

[c] In this study, 25% of patients had removal of at least one nevus with severe nuclear atypia." Some of these were probably melanoma in situ lesions.

[d] These 16 patients developed 20 melanomas: 8 were in situ and 12 were invasive. Eleven of the 12 invasive melanomas were <0.6 mm thick; the one exception was 1.0 mm thick.

Thus, dysplastic nevus remains a viable clinicopathologic concept, recommendations of the National Institutes of Health Consensus Conference notwithstanding.[108] Its own dermatopathology working group endorsed the concept and provided specific histopathologic criteria for the diagnosis of DN.[109] Numerous subsequent authors have supported the continued use of the term "dysplastic nevus,"[70,104,110,111] making it likely that this term and the biological model of which it is a part[107] are here to stay.

MANAGEMENT RECOMMENDATIONS FOR MELANOMA-PRONE FAMILY MEMBERS

Surveillance guidelines have been formulated for members of melanoma-prone families. These are currently based on expert opinion, using best available clinical judgment.[9,10,17,112,113] Although the preponderance of very thin (i.e., biologically early, potentially curable) melanomas (see Tables 4 and 5) detected as a result of surveillance of high-risk populations provides a basis for optimism that this strategy will reduce melanoma mortality, formal demonstration of a mortality reduction has not yet been documented. Management recommendations employ a two-tiered approach: (1) modification of melanoma risk factors, and (2) surveillance aimed at detection and removal of changing pigmented lesions.

Primary melanoma prevention strategies begin by educating parents and children about the natural history of normal (common, acquired) nevi, dysplastic nevi, and melanoma. Family members may be thereby empowered to participate actively in their own care and to know when to seek medical attention. Principles of sun avoidance and sunburn avoidance also should be emphasized. Staying out of the midday sun, recognition of the special sunburn hazards posed by sunlight reflection off snow and water, and use of appropriate clothing (broad-brimmed hats, lightweight long-sleeved shirts and pants) should be given special attention. Appropriate use of sunscreens with a skin protection factor rating of 15 or more (the product should protect against both ultraviolet [UV]-A and UV-B) is central to photoprotection recommendations for high-risk patients. Sunscreen lotions should be periodically reapplied after swimming or heavy perspiration. These products should *not* be used as a way of extending the amount of time patients spend in the sun; the protection they offer is only relative, and prolonged sun exposure will result in significant UV light reaching the skin in spite of the sunscreen. Children from high-risk families should be taught photoprotection by their parents in early childhood. A fundamental principle is "do not get sunburned," because episodic, intense exposure to the sun in childhood and the teenage years may be a significant melanoma risk factor.[114] Although com-

mon sense would seem to make it unnecessary to say, use of tanning parlors should be forbidden because the UV exposure sustained in that setting is a clearly recognized melanoma risk factor.[115,116] High-risk patients should, if possible, avoid occupational exposure to UV light (e.g., as seen in the use of welding torches and textile drying equipment). Finally, both immunosuppression[117,118] and the use of psoralen plus UV-A (PUVA) in the treatment of psoriasis[119] have been associated with increases in melanoma risk and are best avoided, if possible, in persons at increased genetic risk of melanoma.

The goal of surveillance of high-risk patients is recognition and prompt removal of pigmented lesions that are clinically suggestive of melanoma or that are changing in a worrisome manner. Many of the lesions removed in this manner will *not* be malignant, but a significant proportion will be true melanoma precursors that are progressing toward melanoma, and the removal of which interrupts the tumor progression pathway. Kelly et al.[104] reported removing 10 nevi for every melanoma detected in their prospective survey of DN patients; nearly half (46%) were DN.

High-risk family members should undergo a baseline, head-to-toe skin examination, *including the scalp*, with removal of any lesions that are clinically suggestive of melanoma. Children in these families should have their first skin examination by age 10, or sooner if clinically indicated. Baseline total body photographs should be taken to use as a reference record for follow-up examinations.[120,121] Surveillance for pancreatic cancer is warranted only in families with *CDKN2A* mutations in which at least one pancreatic cancer case has been observed. Similarly, brain tumors should be sought only in families in which such cancers appear to be part of the clinical syndrome.

Family members should be instructed to examine their own skin monthly aided by copies of their skin photographs. The skin should be examined every 3 to 12 months by a health care provider, depending on whether nevi are stable or changing and on the recency of melanoma diagnosis. Some family members have been observed to experience periods of accelerated mole change and new mole development, sometimes (although not invariably) during times of hormonal change such as puberty or pregnancy. Surveillance should be heightened during such times.

Finally, pigmented lesions of concern should be promptly but conservatively excised. Shave biopsy is best avoided in this clinical setting to minimize the risk of incomplete lesion removal and subsequent problems in the histologic interpretation of recurrent pigmentation at a prior biopsy site.[122] For lesions that are not melanoma, all that is required is a rim of normal tissue around the perimeter of the nevus (i.e., negative surgical margins). If a dysplastic nevus has been removed with a negative margin, reexcision of the biopsy site is not required. Do *not* perform a melanoma operation for DN. This represents excessive surgery and unnecessary cosmetic morbidity.

Melanoma-prone family members are often advised to simply have all their nevi prophylactically excised in an effort to eliminate their melanoma risk. In my opinion, this is not advisable for the following reasons. First, in patients with multiple DN, the chance of any single lesion becoming malignant is small. Most, in fact, do *not* become malignant; they simply remain stable. Unfortunately, it is not presently possible to determine a priori which lesions are destined to remain stable and which are destined to progress. Second, careful surveillance permits the clinician to selectively remove only nevi that change. Third, even if all current nevi are removed, new nevi continue to develop; thus, the need for ongoing, periodic skin surveillance is not eliminated by prophylactic surgery. Finally, as the study of Kelly et al.[104]demonstrates, melanomas may arise from clinically normal skin in a significant percentage of patients. Therefore, wholesale, prophylactic removal of all nevi does not avoid the need for continued surveillance of high-risk patients and certainly represents excessive surgery for most patients. The one exception to this general rule is DN on the scalp, which are difficult to monitor because they are hidden by the hair. It would not be unreasonable to routinely remove all such lesions.

Finally, the issue of predictive genetic testing as a tool for managing melanoma-prone family members must be addressed. Testing for mutations in the *CDK4* gene is not commercially available, but the prevalence of mutations at this locus is so extraordinarily low that testing would be useless for most families. Clinical testing for mutations in the *CDKN2A* gene is commercially available but is of uncertain clinical benefit. The sensitivity and specificity of the assay are unknown. Mutations at this locus account for only a small proportion of unselected melanoma families, as described earlier. The American Society of Clinical Oncology has classified hereditary melanoma as among the syndromes in which the significance of a germline mutation is unclear and for which the medical benefit of heterozygote identification is not established.[123] The important message here is that commercial availability of a genetic test does not automatically mean that it is ready for routine clinical application. Thus germline testing for *CDKN2A* mutations is best regarded as a research tool at the present time.

CONCLUSIONS

As one surveys the progress that has been made from the remarkable clinical observation made by William Norris[1] in 1820 to the extraordinary molecular genetic discoveries of the 1990s, it is clear that the study of familial melanoma has come a long way. We now know that there may be at least four genes involved in familial melanoma, and the molecular pathophysiology of two of them (*CDKN2A* and *CDK4*) has been defined. We now know that heredity is an important determinant of nevus phenotype as well and that one particular melanocytic lesion, the dysplastic nevus, is a potent determinant of melanoma risk, both familial and nonfamilial. While we are awaiting more precise understanding of the mechanisms of genetic susceptibility to melanoma (and the gene therapy consequences that will follow), melanoma screening and risk-reduction activities can focus *now* on melanoma family members and people with DN, with the data-based expectation that melanoma morbidity and mortality are likely to decline as a result.

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